This submission is made pursuant to Rules 116 and 129(a). In particular, this application claims benefit of Serial No. 07/580,013, filed September 10, 1990, and this response is the first submission after the Final Office Action, prior to the filing of an appeal brief or abandonment of the application. Accordingly, the applicants are entitled to have the finality of the Office Action withdrawn, and the response considered on the merits. *See* Rule 129(a). A fee of $770.00, as set forth in Rules 129(a) and 17(r), accompanies this response.

Because the Office Action made the rejection of the pending claims final, consideration of this response pursuant to the expedited procedure for response after final rejection set forth in MPEP § 714.13 (8th Ed., Rev. 1, February 2003, pp. 700-209 to 700-210) respectfully is solicited.

REMARKS

Three distinct matters were raised in the Office Action. First, the Examiner withdrew claims 78-99 from consideration, based upon an alleged prior "constructive election." Second, the Examiner rejected claims 62-77 under § 102(e) in view of U.S. Patent No. 5,981,701 (Wallach I). Third, the Examiner rejected claims 62-77 under §102(e) in view of U.S. Patent No. 5,811,261 (Wallach II).

Each of these matters is addressed separately below. For the reasons stated herein, reconsideration of the Patent Office's actions and allowance of all claims is respectfully requested.

Withdrawal Of Claims 78-99

The Patent Office withdrew from consideration claims 78-99, presented in the SUPPLEMENTAL AMENDMENT dated August 7, 2002. The Patent Office asserted that those claims are directed to subject matter that is independent or distinct from the subject matter of examined claims 62-77:

> claims 78-99 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the DNA of claims 78-99 and the receptor protein of claims 62-77 are independent and distinct, each from the other, because they are products which possess characteristic differences in structure and function, and each has an independent use, that is distinct for each invention which cannot be exchanged. In the instant case, nucleic acids and proteins are distinct because their structures and modes of action are different, which require non-coextensive searches, and furthermore, the DNA of claims 78-99 can be used as a hybridization probe, while the protein of claims 62-77 can be used for the production of antibodies or screening of compounds. (Paper No. 41 at 2.)

The Patent Office concluded that "[s]ince applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 78-99 are withdrawn from consideration as being directed to a non-elected invention." (*Id.*)

Contrary to the assertion of the Patent Office, claims 78-99 are not barred from examination based on an alleged constructive election. A constructive election occurs only when the applicant presents an amendment which results in independent or distinct groups of claims, which if examined together, would impose a serious burden on the Examiner without the election. 37 CFR § 1.145 and MPEP § 821.03 (8th Ed., Rev. 1, February 2003, p. 800.63).

Claims 78-99 are drawn to isolated DNA sequences encoding a protein having the amino acid sequence of Figure 1 or fragments thereof (claims 78-85), isolated DNA sequences that comprise the DNA sequence of Figure 1 or fragments thereof (claims 86 and 91-99), isolated DNA sequences encoding a protein having the amino acid sequence encoded by the DNA sequence of Figure 1 beginning at amino acid number 12 and ending at approximately amino acid 180 (87-89), and an isolated DNA sequence encoding the extracellular region of the 55 kD TNF-BP (claim 90). Examined claims 69-77 are directed to proteins having the "amino acid sequence encoded by the DNA sequence of Figure 1 beginning at nucleotide number 121 and ending at approximately nucleotide number 627...." (Claim 69.)

Thus, withdrawn claims 78-99 and previously examined claims 69-77 commonly recite DNA sequences of Figure 1. In order to examine claims 69-77 the Examiner was required to conduct a thorough search of the prior art:

> In the examination of an application for patent, ***an examiner must conduct a thorough search of the prior art***. Planning a thorough search of the prior art requires three distinct steps by the examiner: (A) identifying the field of search; (B) selecting the proper tool(s) to perform the search; and (C) determining the appropriate search strategy for each search tool selected. Each step is critical for a ***complete and thorough search***.
>
> * * *
>
> The search should cover the claimed subject matter and should also cover the disclosed features which might reasonably be expected to be claimed. The field of search should be prioritized, starting with the area(s) where the invention would most likely be found in the prior art. (MPEP § 904.02, 8th Ed., Rev. 1, February 2003, p. 900-51.) (Emphasis added.)

Having already searched the DNA sequences recited in claims 69-77, no additional search would be required to examine claims 78-99. Therefore, no additional burden would be imposed on the Examiner.

Because examination of all the pending claims would not impose a serious burden on the Examiner, the presentation of claims 78-99 was not a constructive election and the withdrawal of claims 78-99 was improper. For this reason, withdrawal of the constructive election and examination of all pending claims is respectfully requested.

In addition, the Patent Office is required to formally issue a restriction requirement if it is alleged that distinct or independent inventions have been presented for prosecution. This, however, has not done by the Patent Office.[1]

"When the PTO requires an applicant to withdraw claims to a patentably distinct invention (a restriction requirement), § 121 shields those withdrawn claims in a later divisional application against rejection over a patent that issues from the original application." *Geneva Pharmaceuticals Inc. v. GlaxoSmithKline PLC*, 68 USPQ2d 1865, 1869 (Fed. Cir. 2003). In *Geneva* the Court recognized the tension that exists between the need for restriction of independent or distinct inventions and the requirement to issue only one patent per invention:

> Section 121 shields claims against a double patenting challenge if consonance exists between the divided groups of claims and an earlier restriction requirement. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1579 (Fed. Cir. 1991) ("Consonance requires that the line of demarcation between the 'independent and distinct inventions' that

[1] If the Patent Office intended to issue a restriction requirement, it is requested to formally issue such requirement on the record so that the restriction requirement may be formally traversed to preserve the applicants' rights under both 35 USC § 121 and 37 CFR §§ 1.143 and 1.144.

> prompted the restriction requirement be maintained.... Where that line is crossed the prohibition of the third sentence of Section 121 does not apply.") (quoting *Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 688 (Fed. Cir. 1990)). If a restriction requirement does not clearly set forth the line of demarcation, then challenged claims could not satisfy the consonance requirement. Therefore ***restriction requirements must provide a clear demarcation between restricted subject matter to allow determination that claims in continuing applications are consonant and therefore deserving of § 121's protections***. *Geneva* at 1871. (Emphasis added.)

Because the Patent Office failed to issue a restriction requirement pursuant 35 USC § 121, the withdrawal of claims 78-99 from consideration should be withdrawn.

Should the Patent Office maintain that the withdrawal of claims 78-99 in Paper No. 41 was intended as a restriction requirement under 35 USC § 121, then the restriction requirement is clearly inadequate and is hereby traversed.

> Under the statute an application may properly be required to be restricted to one of two or more claimed inventions ***only if they are able to support separate patents and they are either independent*** (MPEP § 806.04 - § 806.04(i)) ***or distinct*** (MPEP § 806.05 - § 806.05(i)). (MPEP § 803, (8th Ed., Rev. 1, February 2003, pp. 800-3 to 800-4.)) (Emphasis added.)

The Office Action stated that "the DNA of claims 78-99 and the receptor protein of claims 62-77 are independent and distinct...." (Paper No. 41 at 2.) Beyond the conclusion of distinctiveness, the Patent Office asserted only that "nucleic acids and proteins are distinct because their structures and modes of action are different, which require non-coextensive searches, and furthermore, the DNA of claims 78-99 can be used as a hybridization probe, while the protein of claims 62-77 can be used for the production of antibodies or screening of compounds." (*Id.*)

Merely asserting that claims recite products that have different structures or that may be used for different purposes does not necessarily establish that the claims, as actually recited, are patentably distinct from one another. *See* MPEP § 806.05 - § 806.05(i) (8th Ed., Rev. 1, February 2003, pp. 800-42 to 800-47.) Accordingly, the Patent Office has failed to demonstrate that the proteins of claims 62-77 and the isolated DNA sequences of claims 78-99 are distinct from one another. The restriction requirement is deficient for this reason alone and should be withdrawn.

Furthermore, the Patent Office has failed to provide any evidence that the search and examination of all the claims cannot be made without serious burden. Restriction is improper unless there is a serious burden on the Examiner absent restriction.

> If the search and examination of an entire application can be made without serious burden, ***the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions***. (MPEP § 803 at 800-4.) (Emphasis added.)

Various means may be employed to demonstrate this serious burden:

> For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant. (*Id.*)

The Patent Office did not allege even one of these three criteria. At best, the Patent Office asserted only that the DNA and protein "require non-coextensive searches." As noted above, however, previously searched and examined claims 69-77 are drawn to proteins defined in part by the DNA sequences of Figure 1 that are recited

in the claims. Claims 78-99 are drawn to isolated DNA sequences of Figure 1. Claims 69 and 88 recite exactly the same nucleotides, *i.e.*, nucleotides 121 to 627 of Figure 1. Accordingly, the examination of examined claims 69-77 required the Examiner to search for the nucleotide sequences recited in claims 78-99 and the presentation of those claims requires no additional search.

The Patent Office has not alleged a separate classification, separate status in the art or different field of search for the allegedly distinct inventions. Accordingly, the Patent Office has not shown that the "serious burden" required to support a restriction requirement exists. For this additional reason, the restriction requirement is deficient and should be withdrawn.

Rejection Under § 102(e) Based Upon Wallach I

Claims 62-77 were rejected under 35 U.S.C. § 102(e) as anticipated by Wallach *et al.*, U.S. Patent No. 5,981,701 ("Wallach I"). (Paper No. 41 at 3.) In making the rejection, the Patent Office contended that the claims were rejected "for reasons of record set forth in Paper No. 32, 4/17/2002, and as evidenced by U.S. Patent No. 5,811,261 [("Wallach II")]." (*Id.*)

For the reasons set forth below, the rejection respectfully is traversed.

Wallach I discloses a "substantially purified TNF Inhibitory Protein which can antagonize the effects of TNF." Column 2, lines 45-46. The TNF Inhibitory Protein was obtained from urine. "Partially purified" TNF Inhibitory Protein was obtained by "fractionation of the urinary proteins by gel filtration." *See* column 5, line 48 to column 6, line 20. "Substantially purified" material was obtained using ion (cation and anion)

exchange chromatography and reversed phase high pressure liquid chromatography. See column 7, line 54 to column 9, line 49. Wallach I repeatedly characterizes the TNF Inhibitory Protein as "containing at the N-Terminus the following amino-acid sequence: Asp-Ser-Val-Cys-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-X-Asn-Ser." Column 4, lines 26-33, column 10, lines 21-28; and column 12, lines 12-22.

It is well settled that anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single prior art reference, arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.,* 221 USPQ 481, 485 (Fed. Cir. 1984).

Facially, the rejection here is not based solely on Wallach I or on any other single prior art reference. The Patent Office has conceded, in fact, that Wallach I does not expressly disclose the claimed proteins. The Patent Office has attempted to fill that void with an "inherency" argument based upon the later-in-time Wallach II, which contains disclosure significantly different from Wallach I and which is not prior art.

At bottom, the § 102(e) rejection rests on a strained tautology that mixes, matches and attempts to reconcile applicants' disclosure with the disclosure of Wallach I, "claim 2" of Wallach I and the disclosure of Wallach II. In particular, the Office Action recites:

> The protein of the '701 patent [Wallach I] is 100% identical to the amino acid sequence as set forth in Figure 1 of the instant application, as evidenced by the sequence as set forth in the '261 patent [Wallach II], see SEQ ID NO: 2. In the '701 patent, claim 2 is directed to a purified protein which

> contains the sequence, but that sequence is not claimed as being the N-terminal end of the protein, only that the protein must "contain" the sequence. Thus, the protein set forth in the '701 patent inherently possess the sequence of SEQ ID NO: 2 of the '261 patent even though the full sequence was not set forth until the '261 patent. (Paper No. 41 at 4.)(Emphasis added.)

It is respectfully submitted that the Patent Office has erred both factually and legally by rejecting claims 62-77 over Wallach I "and as evidenced by" Wallach II. As shown below, the written description of Wallach I does not disclose a homogeneous polypeptide falling within the scope of the rejected claims. The reliance by the Patent Office upon "claim 2" of Wallach I is also misplaced, because it is not a description of any polypeptide and is legally incapable of anticipating applicants' claims. Finally, Wallach II is not prior art, is irrelevant, and cannot be used to read into Wallach I disclosure that is plainly not there.

As noted above, the Patent Office concedes that Wallach I does not expressly describe the claimed subject matter. The Patent Office has asserted, however, that Wallach I "inherently possess the sequence of SEQ ID NO:2" of Wallach II (Paper No. 41 at 4.)

It is initially noted that the issue here is not whether Wallach I "inherently" discloses anything disclosed in the later-in-time and non-prior art Wallach II. The dispositive -- only -- issue is whether Wallach I "inherently" discloses something falling within the scope of applicants' claims.

Claim 62 recites a "homogenous" receptor protein with "an apparent molecular weight of about 55 kD on a non-reducing SDS-polyacrylamide gel and ... comprises the amino acid sequence of Figure 1." By contrast, Wallach I discloses a

"substantially purified" 26-28 kD TNF Inhibitory Protein that is repeatedly said to contain a specific "N-terminus," *viz.*, "asp-per-val-sys-pro-gen-gly-lys-tyr-ile-his-pro-gln-x-asn-ser." *See* Col. 8, lines 5-7 and col. 10, lines 1-28. That sequence appears in the claimed polypeptides, but not at the "N-terminus." Instead, that sequence is an internal sequence, beginning at amino acid position 12, downstream from the N-terminus of the mature polypeptide, and even further downstream from the N-terminus of the leader sequence peptide, as shown in Figure 1.

To support an anticipation rejection based on inherency, as here, the Patent Office must provide factual and technical grounds showing that the inherent feature "necessarily flows" from the cited prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990) and *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981) (inherency must flow as a necessary conclusion from the prior art, not simply a possible one.) "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 USPQ2d 1597,1599 (Fed. Cir. 2002).

Simply stated, Wallach I does not anticipate claim 62 "inherently" or otherwise, because it does not identically describe the claimed polypeptide. Wallach I, at best, describes a "substantially" purified fragment that is missing upstream and downstream amino acids, not the "homogeneous" protein having the different and complete sequence recited in the claims. Wallach I does not describe the claimed polypeptides and does not place that subject matter in the possession of the skilled artisan. Accordingly, Wallach I does not disclose each and every element of claim 62 and the rejection must be withdrawn as to claim 62.

Claims 63-65 recite a "homogeneous" protein that "comprises the amino acid sequence of Figure 1 beginning at amino acid number 1 and ending approximately at amino acid number 180...." As noted, Wallach I discloses only the 16 amino acid "N-terminus" of its less-than-fully-purified protein and is absolutely silent as to the internal sequence and COOH-terminal end of the protein. Wallach I does not disclose a protein of the length recited by or the amino acid sequence claimed in claims 63-65. Accordingly, Wallach I does not disclose each and every element of claims 63-65 and the rejection must be withdrawn as to these claims.

Claims 66-68 likewise recite a "homogenous" receptor protein "encoded by the DNA sequence of Figure 1." Claims 67 and 68 further recite that the "protein is recombinantly produced." Wallach I does not disclose a single nucleotide encoding any protein. Wallach I alludes to, but does not describe any particular recombinant method that would produce the particular polypeptide claimed here by applicants. Wallach I discloses a sequence of 16 amino acids and invites the use of that sequence for cDNA screening and recombinant DNA experimentation. This type of invitation to experiment is not a written description and has also been rejected by the Federal Circuit as non-enabling. *Genetech, Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997) ("It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.") Vague reference to prophetic processes does not describe a particular sequence. *Compare In re Bell*, 26 USPQ2d 1529, 1531-32 (Fed. Cir. 1993). Accordingly, Wallach I does not

disclose each and every element of claims 66-68 and the rejection must be withdrawn as to these claims.

Claims 69-77 recite a "homogeneous" protein that has the amino acid sequence "encoded by the DNA sequence of Figure 1 beginning at nucleotide number 121 and ending at approximately nucleotide number 627...." (Claim 69.) Further, claims 70-71, 73-74, and 76-77 recite that the "protein is recombinantly produced." Again, Wallach I discloses only the 16 amino acids found at the "N-terminus" of its protein and provides no DNA sequence whatsoever, not even a partial sequence. Wallach is therefore silent, both in terms of amino acid sequence and DNA sequence, as to the length of the protein and the COOH-terminal sequence. Accordingly, Wallach I does not disclose each and every element of claims 69-77 and the rejection must be withdrawn as to these claims.

The Patent Office committed further factual and legal error by asserting that "claim 2" of Wallach I anticipates applicants' claims. The Patent Office argued, in particular, that "claim 2" of Wallach I generally refers to but does not explicitly require that the recited 16-mer amino acid sequence be positioned at the "N-terminal end of the protein, only that the protein must 'contain' the sequence." (Paper No. 41 at 4.) As shown below, the Federal Circuit has rejected such reasoning, and rejections based on such reasoning, as "plainly indefensible."

The open-ended language of "claim 2" of Wallach I is not a disclosure of <u>any particular</u> protein sequence. At most, claim 2 embraces any and all amino acid sequences -- of any size -- that may "contain" -- anywhere -- the recited 16-mer

fragment. As a matter of law, a claim of such sweeping scope cannot anticipate the particular structurally defined sequences recited in the claims here.

Indeed, the "scope of a patent's claims determines what infringes the patent; it is no measure of what it discloses." *In re Benno*, 226 USPQ 683, 686 (Fed. Cir, 1985). In *Benno*, the Court rejected, as "a plainly indefensible line of reasoning," the PTO's argument that a generic claim of a prior art patent could defeat patentability of a narrower claim simply because the earlier claim was "broad enough" to read on the latter:

> The Board, nevertheless, reached the opposite conclusion by what we consider to be a plainly indefensible line of reasoning. [The claim of the reference], the Board said, "is broad enough to read on [the claimed invention]. That is the appellant's claimed invention, in major part. Therefore, reasoned the Board, that configuration would have been obvious from [the reference], which is a non sequitur.
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> * * *
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> The scope of a patent's claims determines what infringes the patent; it is no measure of what it discloses. A patent discloses only that which it describes, whether specifically or in general terms, so as to convey intelligence to one capable of understanding. While it is true, as the Solicitor suggested at oral argument, that "a claim is part of the disclosure," that point is of significance principally in the situation where a patent application as filed contains a claim which specifically discloses something not disclosed in the descriptive part of the specification ... But that is not the situation here. [The claim] does not disclose any structure additional to what the [] specification discloses. *Id.* at 686-687.

The description of Wallach I makes it clear that the only substantially purified protein that was obtained had an "N-terminus" that is not the N-terminus of the claimed proteins. The repeated characterization in the written description of Wallach I is not altered by and cannot be ignored in view of "claim 2" of Wallach I. Mere silence

in one part of a patent, especially a claim, cannot be construed as a description that departs from or contradicts what is explicitly described, repeatedly, elsewhere in the patent. *Compare In re Evanega*, 4 USPQ2d 1249, 1251 (Fed. Cir. 1987) ("The mere absence of an explicit requirement of isolation of the phases in example 4 cannot reasonably be construed as an affirmative statement that the phases need not be isolated. Instead, the entirety of [the prior art reference] suggests that the phases must be physically isolated.") Wallach I must be read as a whole, and when that is done there is no plausible basis to assert that "claim 2" of Wallach I identically describes the instantly claimed subject matter.

Notwithstanding the lack of relevance with respect to the *dispositive* issue of whether Wallach I "inherently" describes the claimed proteins, it is also noted that the Patent Office provided no evidence to support the assertion that the "protein" of Wallach I "inherently possess the sequence of SEQ ID NO:2" of Wallach II. Wallach II describes different processes and different proteins than are described in Wallach I. Fairly and practically viewed, Wallach II addresses the deficiencies and failures of Wallach I and further shows why Wallach I does not anticipate claims 62-77.

Wallach I discloses the purification of TNF inhibitory protein from human urine by a multistep process. The steps include:

1) preparing a urine concentrate by microfiltration;
2) isolating a crude protein fraction from the urine concentrate by dialyzation;
3) purifying the protein by ion-exchange chromatography in three steps:
    a) carboxymethyl Sepharose chromatography,
    b) cation-exchange mono S HR 5/5 FPLC chromotography, and
    c) anion-exchange mono Q HR 5/5 FPLC chromotography;
4) purifying the protein by reversed phase HPLC; and
5) recovering the purified protein. *See* Col. 7, line 54 - col. 9, line 49.

Wallach I discloses that this process produces a protein with a molecular weight of "about 26-28 kDa on SDS PAGE under reducing conditions." Col. 8, lines 6-7. Wallach I discloses the N-terminal sequence of the purified protein as: Asp-Ser-Val-Cys-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-X-Asn-Ser. *See* Col. 4, lines 26-33; col. 10, lines 21-28; and col. 12, lines 12-22.

Wallach II discloses a recombinant protein, obtained via cloning and other techniques not employed by Wallach II. In particular, the Wallach II method involved:

> i) transfecting eukaryotic cells with an expression vector comprising a DNA molecule encoding the whole type I human TNF receptor or a soluble domain thereof, and
> ii) culturing the transfected cells, whereby the desired protein is produced and secreted into the medium.
> Col. 4, lines 1-9.

Wallach II notes that the "size of the protein encoded by the cDNA (about 50 kD) is significantly larger than that of TBF-I." Col. 9, lines 34-35. SEQ ID NO:2 of Wallach II has an N-terminal sequence of: Ile-Tyr-Pro-Ser-Gly-Val-Ile-Gly-Leu-Val. The N-terminal sequence disclosed in Wallach II is not the same as the N-terminal sequence of Wallach I.

In sum, Wallach I and Wallach II disclose different methods of isolation/production of proteins, which produce proteins with different molecular weights and different amino acid sequences. The Patent Office's conclusions as regards Wallach I and Wallach II are thus clearly erroneous and cannot be relied upon to support the rejection of applicants' claims.

The fact that Wallach I did not "inherently" disclose the protein later cloned in Wallach II is further established by a publication coauthored by the Wallach patentees. Therein, they point out that the chromatographic purification method

employed in Wallach I inherently produced truncated polypeptide fragments, not the homogeneous full length polypeptides claimed by applications. *See Engelmann*, J. Biol. Chem. 265, 1531-1536 (1990) (copy attached hereto):

> When isolated by a multistep chromatographic procedure, the TNF-binding protein turned out to be somewhat smaller than after ligand affinity purification (27,000 compared to about 30,000). . . . A likely explanation for the difference in molecular size is the higher probability for proteolytic degradation in the more lengthy manipulations involved in the chromatographic purification as compared to affinity purification. *Id.* at 1534-35.

On this record, it is manifest that Wallach I does not identically describe the claimed polypeptide. The rejection of claims 62-77 in view of Wallach I should be withdrawn.

Rejection Under §102(e) Based Upon Wallach II

Claims 62-77 were additionally and separately rejected under 35 USC § 102(e) as anticipated by Wallach II. (Paper No. 41 at 5.) For the reasons set forth below, the rejection respectfully is traversed.

Wallach II discloses the production of human Tumor Necrosis Factor Binding Protein I ("TBP-I"), "precursors and analogs thereof, by a method comprising transfection of eukaryotic, preferably CHO, cells with an expression vector comprising a DNA molecule encoding the whole type I human TNF receptor or a soluble domain thereof." Col. 2, lines 23-28. In addition, Wallach II discloses "soluble proteins selected from precursors and analogs of TBP-I, which are secreted into the medium by eukaryotic cells transfected with a DNA molecule encoding the whole human type TNF receptor or a soluble domain thereof." *Id.*, lines 32-36.

In making the rejection, the Patent Office asserted that Wallach II "discloses purification of a tumor necrosis factor inhibitory protein, which interacts with TNF and inhibits the binding of TNF to its receptors and the cytotoxic effects of TNF (column 2 lines 1-3)." (Paper No. 41 at 5.) The Patent Office further asserted that:

> The protein disclosed in the '261 patent has a molecular weight of 40-80 kD (column 9 line 34-35[2]). The full amino acid sequence of the TNF inhibitory protein of Wallach is set forth in the '261 patent (see SEQ ID NO: 2). The sequence of SEQ ID NO: 2 of the '261 patent is 100% identical to the amino acid sequence of the protein claimed in the instant application, and is 100% identical from amino acids 1-180 of the protein claimed in the instant application. (*Id.*)

Wallach II has a filing date of September 24, 1993, which is later in time than applicants' filing date. Wallach II claims priority as a continuation of USSN 07/625,668 (the "'668 application) filed December 13, 1990, which claims priority as a continuation-in-part of USSN 07/243,092 (the "'092 application") filed September 12, 1988, but the Examiner cannot rely on the September 12, 1988 filing date of the '092 application in the present rejection because the subject matter relied upon in the rejection was not described or enabled in the '092 application.

When a rejection relies on an issued U.S. patent claiming benefit to an earlier filed application as a ***continuation-in-part***, it is incumbent upon the Patent Office to make the necessary factual determinations as to whether the subject matter in the patent asserted is supported by the earlier filed application, *i.e.*, complies with the requirements of § 112, first paragraph. 35 USC § 120. *In re Warner*, 154 USPQ 173,

[2] Applicants note that Patent Office has apparently misinterpreted the disclosure of Wallach II on this point. The disclosure the Patent Office points to reads: "The size of the protein encoded by the cDNA (about 50 kD) is significantly larger than that of TBF-I." Accordingly, the TBF-I disclosed by Wallach II is

177 (CCPA 1967), *cert. denied*, 389 U.S. 1057 (1968) (There is a "burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under sections 102 and 103....") Where, as here, the rejection fails to make these factual determinations, the rejection is insufficient as a matter of law and must be withdrawn.

In fact, nothing disclosed in Wallach II is found in Wallach I. Not a single paragraph in Wallach II is found in Wallach I. None of the figures is the same. No sequence disclosed in Wallach II is found in Wallach I, much less the SEQ ID NO:2 of Wallach II, explicitly relied upon by the Patent Office.

Other than the claim to priority, the only reference to the Wallach I application found in Wallach II is at the beginning of the Description of the Invention. "Purified TBP-I isolated from human urine was described in U.S. Ser. No. 07/243,092 of the present applicants and shown to contain at the N-terminus the amino acid sequence shown in FIG. 1Aa." Col. 3, lines 58-61. That reference does not, however, demonstrate that the subject matter of Wallach II is described or enabled, much less both, by the disclosure of Wallach I.

The actual production and isolation of a protein by recombinant methods disclosed and claimed in Wallach II is completely different from the method of isolation and purification of a protein disclosed in Wallach I. There is no written description or enabling disclosure in Wallach I for the methods of protein production and purification of Wallach II. Accordingly, Wallach II is only entitled to claim priority back to the filing

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significantly smaller than 50 kD. Moreover, there is no disclosure of a range of molecular weights of 40-80 kD of any protein in Wallach II.

date of the C-I-P application in which the new matter relied upon by the Patent Office was added, December 13, 1990.

Accordingly, Wallach II cannot be relied upon by the Patent Office in making a rejection for anticipation, and the rejection should be withdrawn.

Pursuant to 37 C.F.R. §§ 1.56, 1.97 and 1.98, applicants respectfully direct the attention of the Patent Office to the documents listed on enclosed Form PTO-1449. Documents B15, C35 and C36 listed on Form PTO-1449 are enclosed. Also enclosed is a Statement in Support of the Opposition dated December 30, 2003 (and related filing papers), issued by the European Patent Office in the corresponding application. The documents listed above have previously not been considered by the Patent Office.

Consideration of all the documents cited on Form PTO-1449 is requested.

SUMMARY

For the reasons set forth above, withdrawal of the constructive election, withdrawal of the rejections, and allowance of the claims are respectfully requested. If the Patent Office has any questions regarding this paper, please contact the undersigned.

No fee, other than the $770.00 fee for filing under Rule 129, the $950.00 fee for a three-month extension of time, and the $180.00 fee for consideration of an Information Disclosure Statement after three months is due. If any fee is deemed necessary, the Commissioner is hereby authorized to charge payment of any additional

fees associated with this communication or credit any overpayment to Deposit Account No. 08-2525.

Respectfully submitted,

By:_____

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